

Clobazam for the Treatment of Lennox-Gastaut Syndrome

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Clobazam (CLB), a 1,5-benzodiazepine, is approved for the treatment of anxiety and/or the adjunctive treatment of epilepsy in more than 100 countries, but is not approved in the United States. Its anticonvulsant effects were first reported by Gastaut in 1978 and approximately 20 studies including more than 300 patients have described the use of CLB in Lennox-Gastaut Syndrome (LGS). In 2005, Lundbeck Inc. (formerly Ovation Pharmaceuticals) began development of CLB for the treatment of LGS. A Phase 2 study, a Phase 3 study and an open-label study were undertaken. The Phase 2 study was a randomized, double-blind, dose-ranging study where patients 2-30 years of age with LGS received either low dose (0.25 mg/kg/day) or high dose (1.0 mg/kg/day) CLB with maximum doses of 10 or 40 mg/day, respectively. The study consisted of a 4-week baseline, 3-week titration and 4-week maintenance period. The primary efficacy variable was the percent reduction in the rate of weekly drop seizures from the baseline period to the maintenance period. Sixty-eight subjects were randomized (low dose, n=32; high dose, n=36). Treatment with both low- and high-dose CLB significantly reduced the weekly drop seizure rate from baseline to maintenance. The median (range) reduction in drop seizure rates was 41% (-531%-100%) (p=0.0162) for the low dose and 93% (48%-100%) (p<0.0001) for the high dose. Thirty-eight percent of low dose patients and 83% of high dose patients achieved \geq 50% reduction in seizure frequency. The most frequently reported AEs were somnolence (n=11, 16%) and lethargy (n=7, 10%). A total of 5 serious AEs were reported in 4 patients. In the low dose group one patient experienced sleep apnea syndrome. In the high-dose group one patient had respiratory distress, one had aspiration and one had constipation and pyrexia. The results of the Phase 2 study suggest that CLB is efficacious in the prevention of drop seizure in LGS. No safety concerns, others than those shared by the class of benzodiazepines, have appeared. Therefore, based on available data, clobazam has an acceptable benefit-risk profile in the treatment of patients with LGS. The Phase 3 randomized, multi-dose placebo-controlled study has completed enrollment and will be used to confirm these results and support an FDA filing for the use of CLB as adjunctive treatment for LGS.